

# Long-term Follow Up in Gene Transfer Studies



# Serious Adverse Events

1999      University of Pennsylvania  
Multi-system failure  
Acute SAE

2002      Necker Hospital for Sick Children – Paris  
T-cell leukemia  
Late-appearing SAE



FDA currently requires applicants for all gene transfer INDs whose protocols were approved after October 1, 2001 to describe their plan to comply with the BRMAC recommendations:



- Provide annual physical examinations for the first 5 years following infusion of the vector or vector-treated cells
- Acquire data annually for years 6-15 via mailed questionnaires regarding
  - Autoimmune, hematopoietic or neurological disease or new malignancies
- Participants in retroviral studies
  - Check for RCR q 3 months during the first year
  - Archive blood annually thereafter
- Send data to the FDA



# FDA currently requires investigators holding INDs for retroviral transduction of hematopoietic stem cells to:

- Provide life-long annual clinical evaluations
- Perform laboratory studies to detect the development of clonal cell populations
  - semi-annually for 5 years
  - then annually for the following 10 years
  - if clonality observed, integration site should be determined
    - If predominant integration is observed 2<sup>nd</sup> test should be performed at interval no more than 3 months later.
- All data would be sent to the FDA



- Compliance with these guidelines is relatively straightforward when the supporting grant is active and remains funded.
- However, when the grant ends it becomes more challenging to ensure proper follow up.



# NIH Notice of Grant Awards for clinical gene transfer studies will state, in part:

“.....The NIH acknowledges that the clinical gene therapy protocol to be supported by this award will require an Investigational New Drug (IND) number and that the Food and Drug Administration currently requires that all recipients of a gene transfer product be followed clinically for 15 years.



“Should this grant expire prior to completion of the required follow up, the National Institutes of Health will facilitate efforts of the principal investigator-sponsor and his/her grantee institution to meet their regulatory responsibilities by offering support for follow up visits for these patients when examined at a General Clinical Research Center (GCRC).....”





- The purpose of the *NIH Guide* Notice was to alert investigators and their institutions to this plan.
- The wording is advisory
  - To emphasize and remind the grantee of its responsibility to follow the FDA guidelines
  - To suggest that the institution make every effort to provide follow up care even after the grant terminates.



National Center for Research Resources  
(NCRR/NIH) will cover the cost of seeing  
such patients if the visits occur on a General  
Clinical Research Center.

- A GCRC could be at the grantee institution or  
at another institution.



# The GCRC would provide

- Outpatient clinic space
- Nursing
- Relevant routine laboratory tests
- Phlebotomy and shipment of blood for assay and/or storage

It would be the responsibility of the grantee institution to contact the patient and to provide support for travel to the GCRC.



- This support by NCRR is not meant to continue the originally funded research activities.
- It is meant to provide a means for follow up after the grant has ended.



The Indiana University National Gene Vector Laboratory (NGVL) will serve as the site for

- long-term blood sample storage
- clonality testing

NCRR will cover the costs associated with storage and clonality testing by supplements to the NGVL cooperative agreement.



- NCRR plans to provide this service for all clinical gene transfer protocols.
- Should such patients be followed outside of a GCRC, it will be the responsibility of the institution to support this through internal, private or other sources of funding.



We anticipate that the FDA would receive

- Documentation of visits
- Data acquired during the visit

The funding IC would not receive these data  
from the sponsor/investigator



NCRR coverage of GCRC use will not be provided if the trial had been industry-sponsored.

Although a GCRC could be used in such industry-sponsored instances, it would be the responsibility of the institution to obtain reimbursement from the sponsor according to GCRC Guidelines.





Principal investigators should use the consent process to inform the participants of the requirements and the processes involved in conducting the long-term follow up studies.



The purpose of this initiative is to help protect patients by detecting adverse events that arise long after their participation in a gene transfer protocol and grant support has ended.



NIH Notice of Grant Award comment for long-term follow up is available at:

**<http://grants.nih.gov/grants/guide/notice-files/NOT-RR-04-005.html>**

Applications for storage or clonality testing at the Indiana University NGVL are available at:

**<http://www.ngvl.org>**

GCRC Guidelines are available at:

**<http://www.ncrr.nih.gov>**

